FGFR3 gene

fibroblast growth factor receptor 3

Normal Function

The *FGFR3* gene provides instructions for making a protein called fibroblast growth factor receptor 3. This protein is part of a family of four fibroblast growth factor receptors that share similar structures and functions. These proteins play a role in several important cellular processes, including regulation of cell growth and division (proliferation), determination of cell type, formation of blood vessels (angiogenesis), wound healing, and embryo development.

The FGFR3 protein spans the cell membrane, so that one end of the protein remains inside the cell and the other end projects from the outer surface of the cell. This positioning of the protein allows it to interact with specific growth factors outside the cell and to receive signals that control growth and development. When these growth factors attach to the FGFR3 protein, the protein is turned on (activated), which triggers a cascade of chemical reactions inside the cell that instruct the cell to undergo certain changes, such as maturing to take on specialized functions.

Several versions (isoforms) of the FGFR3 protein are produced from the *FGFR3* gene. The different isoforms are found in various tissues of the body and they interact with a variety of growth factors. Many isoforms are found in the cells that form bones. Researchers believe that the FGFR3 protein in bone cells regulates bone growth by limiting the formation of bone from cartilage (a process called ossification), particularly in the long bones. One particular isoform of the FGFR3 protein is found specifically in cells that line the surfaces of the body (epithelial cells), including the cells that form the outermost layer of skin, called the epidermis.

Health Conditions Related to Genetic Changes

achondroplasia

Two mutations in the *FGFR3* gene cause more than 99 percent of cases of achondroplasia, which is a form of short-limbed dwarfism. Both mutations lead to the same change in the FGFR3 protein. Specifically, the protein building block (amino acid) glycine is replaced with the amino acid arginine at protein position 380 (written as Gly380Arg or G380R). Researchers believe that this genetic change causes the receptor to be overly active, which leads to the disturbances in bone growth that occur in this disorder.

bladder cancer

Some gene mutations are acquired during a person's lifetime and are present only in certain cells. These changes, which are called somatic mutations, are not inherited. Somatic mutations in the *FGFR3* gene are associated with some cases of bladder cancer. These mutations overactivate the FGFR3 protein, which likely directs bladder cells to grow and divide abnormally. This uncontrolled cell division leads to the formation of a bladder tumor.

Somatic mutations in the *FGFR3* gene are associated with bladder cancer when they occur only in bladder cells. These same mutations cause the skeletal disorder thanatophoric dysplasia when they are inherited from a parent (and occur in all of the body's cells).

Crouzonodermoskeletal syndrome

A single *FGFR3* gene mutation has been identified in people with Crouzonodermoskeletal syndrome, which is a condition that causes premature closure of the bones of the skull (craniosynostosis), leading to a misshapen head and distinctive facial features, and skin abnormalities. The genetic change that causes this condition replaces the amino acid alanine with the amino acid glutamic acid at position 391 of the FGFR3 protein (written as Ala391Glu or A391E). Researchers have not determined how this mutation leads to the signs and symptoms of this disorder, but the altered receptor appears to disrupt the normal growth of skull bones and affect skin pigmentation.

epidermal nevus

Mutations in the *FGFR3* gene have been found in approximately 30 percent of people with a certain type of epidermal nevus (plural: nevi). Specifically, *FGFR3* gene mutations are associated with some keratinocytic epidermal nevi, which are abnormal skin growths that are composed of skin cells called keratinocytes. *FGFR3* gene mutations have not been found in other types of epidermal nevi.

The most common *FGFR3* gene mutation in epidermal nevi changes a single amino acid in the FGFR3 protein. The amino acid arginine is replaced with the amino acid cysteine at position 248 (written as Arg248Cys or R248C). This mutation creates a protein that is turned on without attachment of a growth factor, which means that the FGFR3 protein is constantly active. Studies suggest that cells with this *FGFR3* gene mutation grow and divide more than normal cells. The resulting overgrowth of skin cells leads to epidermal nevi.

The *FGFR3* gene mutations found in epidermal nevi also occur in people with another skin abnormality called seborrheic keratosis and in people with thanatophoric dysplasia, Crouzonodermoskeletal syndrome, and SADDAN (each described in another section on this page). However, in contrast with the skeletal conditions, the mutations associated with epidermal nevi are somatic mutations that arise randomly

during the early stages of development before birth. The mutations are present only in the cells of the nevus, not in the normal skin cells surrounding it.

hypochondroplasia

At least 20 mutations in the *FGFR3* gene have been identified in people with hypochondroplasia, another form of short-limbed dwarfism that is milder than achondroplasia. Many cases are caused by one of two specific *FGFR3* gene mutations, both of which lead to the same change in the FGFR3 protein. Specifically, the amino acid asparagine is replaced with the amino acid lysine at protein position 540 (written as Asn540Lys or N540K). Other *FGFR3* gene mutations probably cause a small number of cases of hypochondroplasia. Although the effects of these mutations have not been explained, they probably cause the receptor to be mildly overactive, which leads to the disturbances in bone growth that occur in this disorder.

lacrimo-auriculo-dento-digital syndrome

At least one mutation in the *FGFR3* gene has been found to cause lacrimo-auriculo-dento-digital (LADD) syndrome. The main features of LADD syndrome are abnormal tear production, malformed ears with hearing loss, decreased saliva production, small teeth, and hand deformities. The *FGFR3* gene mutation that causes LADD syndrome replaces the amino acid aspartic acid with the amino acid asparagine at position 513 in the FGFR3 receptor protein (written as Asp513Asn or D513N). This mutation most likely reduces the ability of the FGFR3 receptor protein to trigger chemical reactions within cells when bound to its growth factor. These defects in cell signaling disrupt cell maturation and development, which results in abnormal formation of the ears, skeleton, and glands in the eyes and mouth in people with LADD syndrome.

Muenke syndrome

A single mutation in the *FGFR3* gene has been shown to cause Muenke syndrome, which is a condition that causes craniosynostosis, leading to a misshapen head and distinctive facial features. The mutation that causes this condition substitutes the amino acid arginine for the amino acid proline at position 250 in the FGFR3 protein (written as Pro250Arg or P250R). This mutation results in the production of a receptor that is overly active, which allows the bones of the skull to fuse sooner than normal.

The Pro250Arg mutation has also been identified in some people with apparently isolated coronal craniosynostosis. This condition is characterized by a premature fusion of the growth line that runs across the top of the head from ear to ear (the coronal suture). People with isolated coronal craniosynostosis do not have the other features of Muenke syndrome, such as hearing loss, hand and foot abnormalities, or developmental delay.

multiple myeloma

SADDAN

One mutation in the *FGFR3* gene has been identified in people with SADDAN (severe achondroplasia with developmental delay and acanthosis nigricans). SADDAN is characterized by short-limb dwarfism (achondroplasia); profound developmental delay; and thick, dark, velvety skin. The genetic change that causes this condition substitutes the amino acid methionine for the amino acid lysine at position 650 of the FGFR3 protein (written as Lys650Met or K650M). Researchers believe that this mutation strongly overactivates the FGFR3 protein, which leads to severe problems with bone growth. It remains uncertain how the mutation causes developmental delay or acanthosis nigricans.

thanatophoric dysplasia

Mutations in the *FGFR3* gene have been identified in people with thanatophoric dysplasia, which is a severe skeletal disorder characterized by extremely short limbs and a narrow chest. At least 10 *FGFR3* gene mutations have been found to cause type I thanatophoric dysplasia. Most of these mutations change a single amino acid in the FGFR3 protein. The most common mutation substitutes the amino acid cysteine for the amino acid arginine at protein position 248 (written as Arg248Cys or R248C). Other mutations cause the protein to be longer than normal.

Only one mutation has been shown to cause type II thanatophoric dysplasia. This mutation replaces the amino acid lysine with the amino acid glutamic acid at position 650 of the FGFR3 protein (written as Lys650Glu or K650E). This change affects a different part of the FGFR3 protein than the mutations that cause type I thanatophoric dysplasia.

The genetic changes responsible for both types of thanatophoric dysplasia cause the FGFR3 receptor to be overactive, which leads to the severe problems with bone growth that occur in this condition.

other cancers

In addition to bladder cancer, somatic mutations in the *FGFR3* gene have been associated with a cancer of white blood cells (multiple myeloma) and cervical cancer. Some cases of multiple myeloma are related to a rearrangement of genetic material (a translocation) involving chromosome 14 and the region of chromosome 4 containing the *FGFR3* gene. Mutations that have been associated with cervical cancer are changes in single nucleotides in the *FGFR3* gene.

FGFR3 gene mutations that lead to multiple myeloma and cervical cancer are thought to overactivate the FGFR3 protein in certain cells. The mutated receptor directs the cells to grow and divide in the absence of signals from outside the cell. This uncontrolled division can lead to the overgrowth of cancer cells.

other disorders

At least two *FGFR3* gene mutations have been found to cause a rare disorder called camptodactyly, tall stature, hearing loss syndrome (CATSHL syndrome). Individuals with this condition are taller than average and typically have hearing loss. They can also have permanently bent fingers or toes (camptodactyly) and other skeletal abnormalities. Researchers suggest that the *FGFR3* gene mutations involved in CATSHL syndrome reduce the function of the FGFR3 protein, although it is unclear how the mutations lead to the signs and symptoms of the condition.

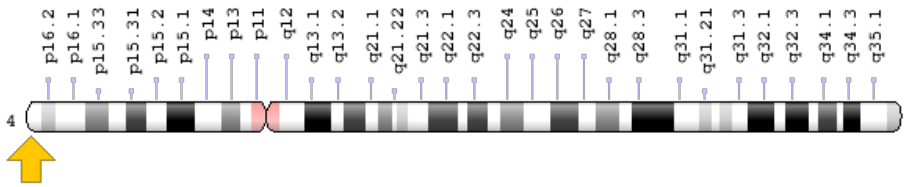
Mutations in the *FGFR3* gene have been found in 30 to 70 percent of people with seborrheic keratoses, which are small, dark, noncancerous (benign) tumors of the skin caused by overgrowth of skin cells. Seborrheic keratoses develop in adulthood and are seen in a majority of people older than age 50. The *FGFR3* gene mutations associated with seborrheic keratosis are somatic mutations and are not inherited. At least nine *FGFR3* gene mutations have been identified in people with seborrheic keratoses. These mutations change single amino acids in the FGFR3 protein. The mutated FGFR3 proteins are abnormally active, which results in the overgrowth of skin cells, leading to seborrheic keratosis. It has been suggested that the mutations involved in seborrheic keratosis may be caused by exposure to ultraviolet (UV) light.

The somatic Arg248Cys *FGFR3* gene mutation found in epidermal nevus (described above) can also cause Garcia-Hafner-Happle syndrome (also known as fibroblast growth factor receptor 3 epidermal nevus syndrome). This condition is characterized by a soft, velvety keratinocytic epidermal nevus and neurological problems, such as seizures, intellectual disability, underdevelopment of the tissue that connects the two halves of the brain (corpus callosum), and a loss of brain cells (cortical atrophy). It is thought that the neurological problems occur because the somatic mutation affects brain cells in addition to those in the skin.

Chromosomal Location

Cytogenetic Location: 4p16.3, which is the short (p) arm of chromosome 4 at position 16.3

Molecular Location: base pairs 1,793,299 to 1,808,872 on chromosome 4 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- ACH
- CD333
- CEK2
- FGFR-3
- FGR3_HUMAN
- fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism)
- HBGFR
- hydroxyaryl-protein kinase
- JTK4
- tyrosine kinase JTK4

Additional Information & Resources

GeneReviews

- Achondroplasia
  https://www.ncbi.nlm.nih.gov/books/NBK1152
- FGFR-Related Craniosynostosis Syndromes
  https://www.ncbi.nlm.nih.gov/books/NBK1455
- Hypochondroplasia
  https://www.ncbi.nlm.nih.gov/books/NBK1477

- Muenke Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1415
- Thanatophoric Dysplasia
  https://www.ncbi.nlm.nih.gov/books/NBK1366

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28FGFR3%5BTI%5D%29+OR+%28fibroblast+growth+factor+receptor+3%5BTI%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D

OMIM

- CERVICAL CANCER
  http://omim.org/entry/603956
- FIBROBLAST GROWTH FACTOR RECEPTOR 3
  http://omim.org/entry/134934
- KERATOSIS, SEBORRHEIC
  http://omim.org/entry/182000
- MYELOMA, MULTIPLE
  http://omim.org/entry/254500

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/FGFRID99.html
- Cancer Genetics Web
  http://www.cancerindex.org/geneweb/FGFR3.htm
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=FGFR3%5Bgene%5D
- HGNC Gene Family: CD molecules
  http://www.genenames.org/cgi-bin/genefamilies/set/471
- HGNC Gene Family: I-set domain containing
  http://www.genenames.org/cgi-bin/genefamilies/set/593
- HGNC Gene Family: Receptor Tyrosine Kinases
  http://www.genenames.org/cgi-bin/genefamilies/set/321

- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=3690
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/2261
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